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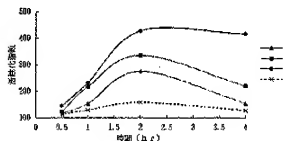
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(54) 【発明の名称】 皮膚外用剤

(57) 【要約】

【課題】 保湿作用、角化正常化作用及び真皮線維芽細胞活性化作用が相乗的に増強され且つ持続的であり、有効な皮膚の老化症状の改善、防止作用、肌荒れ改善作用及び美肌作用を旨し、さらに低刺激性を示す皮膚外用剤を得る。

【解決手段】 2-ヒドロキシ脂肪酸の1種又は2種以上、水酸化アルカリ溶液を作用させて異性化させた糖の混合物、キトサン及びその誘導体より選択される1種又は2種以上、及びアミノ酸及びその誘導体の1種又は2種以上を含有させる。2-ヒドロキシ脂肪酸として炭素数2〜10のもの、水酸化アルカリ溶液を作用させて得る異性化糖混合物としては、グルコース又はラクトースの異性化物或いはこれらの混合物、アミノ酸としてはグリシン、L-アラニン、L-セリン、L-スレオニン、L-アスパラギン酸、L-グルタミン酸、L-アルギニン、L-リジン、L-トリプトファン、L-プロリン、グリシルグリシン及びトリメチルグリシンが好ましい。



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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention]A moisturizing action, a cornification normalizing effect, and a cutis fibroblast activation operation are enhanced synergistically, and this invention is continuous, has an improvement of the effective aged symptoms of the skin, a prevention operation, a surface deterioration improving action, and a lustrous skin operation, and relates to the skin external preparations in which low-stimulus nature is shown further. It is related with the skin external preparations containing one sort of one sort chosen from the mixture of the sugar which one sort of 2-hydroxyfatty acid or two sorts or more, and a hydroxylation alkali solution were made to act, and was made to isomerize in more detail, chitosan, and its derivative or two sorts or more, amino acid, and its derivative, or two sorts or more.

[0002]

[Description of the Prior Art]2-hydroxyfatty acid has the effect outstanding to the improvement of the keratonosis of the skin, moreover -- it is reported by Mr. Eugene Jay Van Scott and others that cutis fibroblast is activated and aged symptoms, such as wrinkles of the skin and a stain, can be improved (Cutis43(3) 222-228 (1989).) Skin external preparations, such as cosmetics containing them, such as JP,H5-139947,A, are also marketed.

[0003]However, when it was going to improve aged symptoms, such as wrinkles of the skin, and a stain, effectively for a short period of time, 2-hydroxyfatty acid needed to be blended quite so much, and the manifestation of skin irritation had become a problem. In obtaining an effective operation from an operation of 2-hydroxyfatty acid being transient, it needed to apply to the skin repeatedly on the 1st, and had resulted in getting worse being not only complicated but a skin stimulus reaction.

[0004]

[Problem(s) to be Solved by the Invention]Then, in this invention, while reducing the content of 2-hydroxyfatty acid as much as possible, The skin irritation was eased and the moisturizing action, the cornification normalizing effect, and the cutis fibroblast activation operation were enhanced synergistically, and it is continuous and aimed at obtaining the skin external preparations which have an improvement of the effective aged symptoms of the skin, a prevention operation, a surface deterioration improving action, and a lustrous skin operation.

[0005]

[Means for Solving the Problem]As a result of examining many things, in order to solve above-mentioned

SUBJECT this invention persons, By using together with 2-hydroxyfatty acid chitosan, the derivative and amino acid of sugar which a hydroxylation alkali solution was made to act and was made to isomerize, and its derivative, and making them contain, [a mixture,] A moisturizing action, a cornification normalizing effect, and a cutis fibroblast activation operation improve and continue synergistically, Loadings of 2-hydroxyfatty acid required to acquire an effective effect can be reduced substantially, and it finds out that a surface deterioration improving action and a lustrous skin operation further exceeding prediction are obtained, and came to complete this invention.

[0006] That is, this invention makes a skin external-preparations base contain one sort of one sort chosen from a mixture of sugar which one sort of 2-hydroxyfatty acid or two sorts or more, and a hydroxylation alkali solution were made to act, and was made to isomerize, chitosan, and its derivative or two sorts or more, amino acid, and its derivative, or two sorts or more, and changes.

[0007]

[Function] In this invention, the improvement in synergistic of the synergistic and continuous activation operation of fibroblast obtained by concomitant use of each constituent and a keratin removal action is shown below.

[0008] First, seeding of the Homo sapiens origin fibroblast is carried out to 96 hole microplate so that it may become a 2.0×10^4 individual per one well, It cultivated at 37 °C by the Dulbecco correction basic nutrient medium (DMEM) containing fetal calf serum of 1.0 capacity % which added each sample shown in Table 1 in 24 hours so that it might become the last concentration shown in front [the]. Exchange for DMEM which contains 2-(4,5-dimethyl-2-thiazolyl)-3,5-diphenyl tetrazolium bromide (MTT) 20 microg/ml in [0.5, 1, 2] a culture start and 4 hours, and it cultivates at 37 °C for 2 hours, The formazan produced by the ring breakage of a tetrazolium ring was measured with the absorbance at 560 nm. The system cultivated by the 1.0 capacity % fetal-calf-serum addition DMEM was considered as contrast, and the system cultivated by the 5.0 capacity % fetal-calf-serum addition DMEM was made into positive control. The relation between the activation index which expressed the absorbance in contrast as 100.0, and the culture time in the inside of the culture medium containing each sample showed the result to drawing 1. Applying the isomerized sugar mixture in Table 1 to the example of manufacture mentioned later, the presentation is as being shown in Table 2.

[Table 1]

| 試料 | 成 分 | 最 終 濃 度 |
|----|---|--|
| 1 | 2-ヒドロキシ酢酸 | 0.1 mM |
| 2 | 2-ヒドロキシ酢酸 異性化糖混合物 | 0.1 mM 0.005 重量% |
| 3 | 2-ヒドロキシ酢酸 異性化糖混合物 キトサン (分子量 10,000) グリシン | 0.1 mM 0.005 重量% 0.001 μM 10.0 mM |

[Table 2]

| 成 分 | 含有量 (重量%) |
|-----------|-----------|
| ブシコース | 0.5 |
| D-グルコース | 0.2 |
| マンノース | 3.6 |
| フルクトース | 37.0 |
| L-グルコース | 53.3 |
| ガラクトース | 1.3 |
| ラクトース縮合物質 | 0.9 |
| ラクトース | 2.5 |

[0009]In drawing 1, when the sample 1 only containing 2-hydroxyacetic acid was added, to (1), the activation index became the maximum (275.4) in [of culture] 2 hours, and it was decreasing after it. When the sample 2 containing 2-hydroxyacetic acid and an isomerized sugar mixture was added, the activation index was too set to (2) with the maximum 2 hours after culture, but as for the activation index, enhancement of 336.3 and a fibroblast activity-ized operation was accepted. On the other hand, when the sample 3 containing 2-hydroxyacetic acid, an isomerized sugar mixture, chitosan, and a glycine was added, the activation index amounted to 427.8, and it was highly maintained by (3), without falling 4 hours after culture. That is, when 2-hydroxyfatty acid, the isomerized sugar mixture, the chitosan, and the amino acid which are the essential ingredients of this invention were contained, activation of fibroblast being reinforced synergistically and becoming durability was shown. Also about positive control (4), the activation index became the maximum (157.5) 2 hours after culture.

[0010]Subsequently, the keratin removal action was evaluated by making into a sample the solution containing the ingredient shown in Table 3. Evaluation makes one group ten patients who present the hyperkeratosis, and with a blind each sample solution of Table 3 in each group A bis die, You made it use 0.5 ml at a time for a wrist glove part for one week, and it carried out by microscope observation comparing about the specimen which carried out tape stripping and extracted the state of the horny layer before the beginning of using and after the end of use. The degree of multiplex exfoliation estimated the state of the horny layer, it was mark-ized in accordance with the judging standard shown in Table 4, and was shown in Table 5 in quest of ten persons' average value.

[Table 3]

| 試料 | 成分 | 濃度 ((w/v)%) |
|----|------------------|-------------|
| 1 | 2-ヒドロキシ酢酸 | 0.01 |
| 2 | 異性化糖混合物 | 1.00 |
| 3 | キトサン (分子量10,000) | 0.10 |
| 4 | グリシン | 0.10 |
| 5 | 2-ヒドロキシ酢酸 | 0.01 |
| | 異性化糖混合物 | 1.00 |
| 6 | 2-ヒドロキシ酢酸 | 0.01 |
| | キトサン (分子量10,000) | 0.10 |
| 7 | 2-ヒドロキシ酢酸 | 0.01 |
| | グリシン | 0.10 |
| 8 | 2-ヒドロキシ酢酸 | 0.01 |
| | 異性化糖混合物 | 1.00 |
| | キトサン (分子量10,000) | 0.10 |
| | グリシン | 0.10 |

[Table 4]

| 多重剝離度 | 評価点 |
|------------|-----|
| ほとんど認められない | 0 |
| わずかに認められる | 1 |
| かなり認められる | 2 |
| 顕著に認められる | 3 |

[0011]

[Table 5]

| 試料 | 使用前 | 使用后 |
|----|-----|-----|
| 1 | 2.9 | 1.7 |
| 2 | 2.9 | 2.5 |
| 3 | 2.8 | 2.6 |
| 4 | 2.7 | 2.2 |
| 5 | 2.9 | 1.6 |
| 6 | 2.8 | 1.7 |
| 7 | 2.8 | 1.4 |
| 8 | 2.8 | 0.7 |

In the sample 8 spreading group containing 2-hydroxyacetic acid, the isomerized sugar mixture, the chitosan, and the glycine which are the essential ingredients of this invention, so that more clearly than Table 5. The degree of multiplex exfoliation of the keratin after use improves notably, and it was shown that the keratin accumulated without exfoliating by superfluous hyperkeratosis is removed good. On the other hand, although the improvement of the degree of keratin multiplex exfoliation was accepted in the sample 5 - sample 7 use group containing the sample 1 which contains 2-hydroxyacetic acid independently, and each of 2-hydroxyacetic acid, an isomerized sugar mixture, chitosan, and a glycine, Compared with the sample 8 use group, it was [the extent] low, and the improvement of the significant degree of keratin multiplex exfoliation was not accepted in the sample 2 - sample 4 use group which contain an isomerized sugar mixture, chitosan, and a glycine by each independent one.

[0012]

[Embodiment of the Invention] In this invention, the thing of the carbon numbers 2-10 can use it preferably as 2-hydroxyfatty acid. For example, 2-hydroxyacetic acid (glycolic acid), 2-hydroxypropionic acid (lactic acid), 2-hydroxybutanoic acid (2-hydroxybutyric acid), 2-hydroxypentanoic acid (2-hydroxyvaleric acid), 2-hydroxyhexanoic acid (2-hydroxycaproic acid), 2-hydroxyheptanoic acid (2-hydroxyenanthic acid), 2-hydroxyoctanoic acid (2-hydroxycaprylic acid), 2-hydroxynonanoic acid (2-hydroxypelargonic acid), the straight chain saturated fatty acid that has a hydroxyl group in the 2nd place called 2-hydroxydecanoic acid (2-hydroxycapric acid), 2-hydroxy propenoic acid (2-hydroxyacrylic acid), 2-hydroxy-trans-2-butene acid (2-hydroxycrotonic acid), 2-hydroxy-cis-2-butene acid (2-hydroxy isocrotonic acid), 2-hydroxy-2-hexene acid, 2-hydroxy-3-hexene acid, 2-hydroxy-4-hexene acid, 2-hydroxy-5-hexene acid, 2-hydroxy-2-heptenoic acid, 2-hydroxy-3-heptenoic acid, 2-hydroxy-5-heptenoic acid, 2-hydroxy-6-heptenoic acid, 2-hydroxy-cis-2-octenate, 2-hydroxy-trans-2-octenate, 2-hydroxy-3-octenate, 2-hydroxy-cis-2-noneneacid, 2-hydroxy-trans-2-noneneacid, The straight chain monoene acid which has a hydroxyl group in the 2nd place, such as 2-hydroxy-3-noneneacid, 2-hydroxy-2-decenoic acid, 2-hydroxy-4-decenoic acid, and 2-hydroxy-9-decenoic acid, The dienoic acid which has a hydroxyl group in the 2nd place, such as 2-hydroxy-2,4-hexadiene acid (2-hydroxysorbic acid), 2-hydroxy-3-methylbutanoic acid (2-hydroxy isovaleric acid), 2-hydroxy-2-ethylbutanoic acid, 2-hydroxy-2-methylpentanoic acid, 2-hydroxy-4-methylpentanoic acid (2-hydroxyisocaproic acid), The branched chain fatty acid which has a hydroxyl group in the 2nd place, 2-hydroxy-2-ethylhexanoic acid, 2-hydroxy-7-methyloctanoic acid (2-hydroxy isononanoic acid), etc., The tricarboxylic acid etc. which have a hydroxyl group are mentioned to the 2nd place, the dicarboxylic acid which has a hydroxyl group in the 2nd place, tartaric acid, malic acid, etc., citrate, etc., and one sort or two sorts or more are chosen and used from these. As content in skin external preparations, if pharmaceutical preparation stability, a bioavailability, etc. are taken into consideration, about 0.01 to 5.0 % of the weight is suitable.

[0013] The mixture of the sugar which the hydroxylation alkali solution was made to act and was made to

isomerize which is the second essential ingredient in this invention is a reaction generation mixture obtained by making isomerize sugar with hydroxylation alkali solutions, such as sodium hydroxide and a potassium hydrate.

The things which made especially glucose or lactose isomerize, or these mixtures are used preferably.

These can be manufactured by the method etc. which were indicated in JP,48-1504,B. As content in skin external preparations, if pharmaceutical preparation stability, a bioavailability, etc. are taken into consideration, about 0.01 to 10.0 % of the weight is suitable.

[0014]As the chitosan which is the third essential ingredient in this invention, and its derivative, the 4th class-ized derivatives, such as with a molecular weight of about 10,000 to 100,000 chitosan and partially deacetylated chitin, and N-trimethyl ** chitosan, etc. are mentioned, and one sort or two sorts or more are chosen and used from these. As content in skin external preparations, about 1.0×10^{-6} -1.0 % of the weight is suitable in consideration of the influence of the physical characteristic on pharmaceutical preparation, etc.

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CLAIMS

[Claim(s)]

[Claim 1]Skin external preparations containing one sort chosen from one sort chosen from a mixture of sugar which one sort of 2-hydroxyfatty acid or two sorts or more, and a hydroxylation alkali solution were made to act, and was made to isomerize, chitosan, and its derivative or two sorts or more, amino acid, and its derivative, or two sorts or more.

[Claim 2]The skin external preparations according to claim 1, wherein one sort of 2-hydroxyfatty acid or two sorts or more are chosen from 2-hydroxyfatty acid of the carbon numbers 2-10.

[Claim 3]The skin external preparations according to claim 1 or 2, wherein a mixture of sugar which a hydroxylation alkali solution was made to act and was made to isomerize is chosen from things which made glucose or lactose isomerize, and these mixtures.

[Claim 4]The skin external preparations according to claim 1 to 3, wherein molecular weights of chitosan and its derivative are 10,000-100,000.